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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 10/010,725   | 11/30/2001  | Wely B. Floriano     | 06618-607002        | 4307             |
| 20985  | 7590        | 07/28/2006           | EXAMINER            |                  |
| FISH & RICHARDSON, PC<br>P.O. BOX 1022<br>MINNEAPOLIS, MN 55440-1022 |             |                      |                     | WHALEY, PABLO S  |
| ART UNIT   |             | PAPER NUMBER         |                     |                  |
|  |             | 1631                 |                     |                  |

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| <b><i>Office Action Summary</i></b> | <b>Application No.</b> | <b>Applicant(s)</b> |
|-------------------------------------|------------------------|---------------------|
|                                     | 10/010,725             | FLORIANO ET AL.     |
| <b>Examiner</b>                     | <b>Art Unit</b>        |                     |
|                                     | Pablo Whaley           | 1631                |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

1)  Responsive to communication(s) filed on 28 April 2006.

2a)  This action is **FINAL**.                            2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

4)  Claim(s) 1-6,8-16,29,31 and 36-47 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5)  Claim(s) \_\_\_\_\_ is/are allowed.  
6)  Claim(s) 1-6,8-16,29,31 and 36-47 is/are rejected.  
7)  Claim(s) \_\_\_\_\_ is/are objected to.  
8)  Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are: a)  accepted or b)  objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)  The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)  Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a)  All    b)  Some \* c)  None of:  
1.  Certified copies of the priority documents have been received.  
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a))

\* See the attached detailed Office action for a list of the certified copies not received

**Attachment(s)**

1)  Notice of References Cited (PTO-892)  
2)  Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3)  Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_  
4)  Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_  
5)  Notice of Informal Patent Application (PTO-152)  
6)  Other: \_\_\_\_\_

**DETAILED ACTION**

***CLAIMS UNDER EXAMINATION***

Claims herein under examination are 1-6, 8-16, 29, 31, and 36-45. Claims 17-28, 30, and 32-35 have been cancelled. Claims 46 and 47 are newly added via the amendment filed 4/28/2006..

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied, as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

***CLAIMS UNDER EXAMINATION***

Claims herein under examination are claims 1-6, 8-16, 29, 31, and 36-47. Claims 1, 4, 5, 6, 31, and 36 have been amended. Claims 17-28, 30, and 32-35 have been cancelled.

### **CLAIM REJECTIONS - 35 USC § 101**

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 29, 31, 36-45, 46 and 47 are rejected under 35 U.S.C. 101 because these claims are drawn to non-statutory subject matter.

Claim 29 is directed to a computational model of a ligand-protein complex comprising a computer-readable memory storing data. The data (model) recited in the claims is non-functional descriptive material. Non-functional descriptive material stored on a computer-readable medium is not statutory subject matter (e.g. music stored on a compact disk).

Claim 46 is directed to a computerized method for modeling a ligand-protein binding interaction, respectively, which does not recite either a physical transformation of matter nor a practical application [i.e. concrete, tangible, and useful result]. The claim recites steps directed to providing and using information, identifying and optimizing binding conditions, calculating energy, and selecting ligands, which encompass *in-silico* methods, and thus do necessarily result in a physical transformation of matter. Where a claimed method does not result in a physical transformation of matter, it may be statutory where it recites a concrete, tangible, and useful result (i.e. a practical application). However, as it is unclear what the actual result of the method is intended to be (see also the rejection under 35 USC 112, below), no actual, concrete result is recited in the claims, and the claim is not statutory.

Claims 31, 36-45, and 47 are directed to a computer program product on a computer-readable medium for modeling ligand-protein binding interactions. A computer readable medium encompasses non-physical media, such as carrier waves. As the computer readable medium is

not defined by the specification to be a physical object, the claims are not necessarily directed to a physical product, and are nonstatutory for this reason.

For these reasons, the claims are not statutory. For an updated discussion of statutory considerations with regard to non-functional descriptive material and computer-related inventions, see the Guidelines for Patent Eligible Subject Matter at 1300 OG 142, Annex IV, Nov. 22, 2005.

### **CLAIM REJECTIONS - 35 USC § 112, 2<sup>nd</sup> Paragraph**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These rejections are necessitated by amendment.

Newly added Claims 46 and 47 recite the limitation "scoring function selected from the group consisting of subtracting....AND...subtracting....; and." It is unclear as to exactly what group the scoring function is selected from, as there are no clearly delineated groups recited (e.g. X, Y, OR Z). Clarification is requested.

Newly added Claims 46 and 47 recite the limitation "outputting the selected calculated binding energies as the predicted binding energies for the predicted binding conformations." It is unclear as to exactly what is output (i.e. selected binding energies, predicting binding energies, or predicted binding conformations). Furthermore, it is unclear in what way selected binding energies are output as the predicted binding energies for the predicted binding conformations. Clarification is requested.

## CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 8, 9, 11, 12, 16, 29, 31, 36, 37, 39, 40, 46, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by DeWitte et al. (*J. Am. Chem. Soc.*, 1996, Vol.118, p. 11733-11744).

Applicant's arguments, filed 4/28/2006, that Dewitte et al. do not teach (i) identifying a plurality of preferred binding positions, or (ii) a combination of identifying and optimizing steps. This rejection is maintained for the reasons set forth below.

Regarding argument (i): DeWitte et al. use a program (SMOG) for the evaluation of ligand-protein interactions and energy scoring, as set forth in the previous office action. Moreover, the SMOG program identifies binding positions of a plurality of ligands [Table 1] that are not sterically hindered (i.e. within 70% of the sum of their Van der Waals radii) [p.11736, Col. 1, ¶ 4]. The examiner maintains this is indeed a teaching for identifying a plurality of preferred binding positions, as this is done for multiple fragments.

Regarding argument (ii): The model of Dewitte et al. is used to screen lead candidates based on binding energy and select candidates with the best energy scores [Fig. 5 and p.11737, Col. 2, ¶ 2]. As set forth in detail in the previous office action, Dewitte et al. also teach a Monte Carlo growth algorithm that uses a coarse-grained ligand design search space (p. 11735, Col. 1, Lines 17-23), and temperature (i.e. annealing) dynamics for parameter minimization (i.e. optimized) (Fig. 1, p. 11736). For these reasons, the examiner maintains that Dewitte et al. indeed teaches combination of identifying, optimizing, and selecting steps as required by the instant invention.

Regarding newly added claims 46 and 47: Dewitte et al. teach the a scoring function that incorporates subtraction of "g" values to account for desolvation (i.e. loss of water) [Equation 10], which is a teaching for the "scoring function" limitation in newly added claims 46 and 47. Therefore, DeWitte et al. anticipates instant claims 1-4, 8, 9, 11, 12, 13, 16, 29, 31, 36, 37, 39, 40, 46, and 47.

Claims 1-4, 6, 9, 11, 12, 31, 36, 37, 39, 40, 41, 43, 44 and 45 are rejected under 35 U.S.C. 102(e)(1) as being anticipated by Freire et al. (US 2001/0000807, Filed: Dec. 13, 2000; Priority Date: Jun. 2, 1998).

Applicant's arguments, filed 4/28/2006, that Freire et al. do not teach or suggest (i) simulated annealing as an optimization strategy, (ii) a plurality of binding conformations for each ligand, or (iii) combination of identifying, optimizing, and calculating steps as required by the claimed invention. This rejection is maintained for the reasons set forth below.

In response to argument (i): It is noted Freire et al. do not specifically recite "simulated annealing" algorithm as an optimization strategy. It is also noted that the instant claims recite

“annealing molecular dynamics” and are silent to the term “simulated annealing,” for which a definition was provided by applicant [p.15]. However, Freire et al. disclose a novel algorithm (Woolford) that incorporate a combination of identification, optimization, and selection steps to design ligands with optimal binding affinities.

In response to arguments (ii) and (iii): Freire et al. do indeed teach the identification of potential binding sites, classification of potential binding sites, and selection of optimal potential binding sites [Fig. 3] for each ligand (i.e. a plurality). The binding potential (i.e. binding energy) is calculated from structure-based thermodynamic considerations [071]. Freire et al. also teach an algorithm comprising coarse-grained sorting of ligands based on binding site characteristics, ligand optimization and scoring, and selection of ligands with optimal binding affinity [Fig. 4]. Freire et al. also use of search algorithms aimed at identifying the minima of functions, check van der Waals conditions using the set of effective van der Waals radii, reject conformations that exhibit van der Waals collisions, and calculate Gibbs energy functions only for allowed conformations (i.e. best conformations) [117]. For these reasons, the examiner maintains that Freire et al. indeed teach the several methods selection and optimizing as required by the instantly claimed invention. Therefore Freire et al. anticipate the instant claims 1-4, 6, 9, 11, 12, 31, 36, 37, 39, 40, 41, 43, 44 and 45.

### **CLAIM REJECTIONS - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

#### **NEWLY APPLIED REJECTION**

Claims 1-6, 8-12, 15, 16, 29, 31, 36-40, and 43-45 are rejected under the first paragraph of 35 USC § 103(a) as being unpatentable over Zuo et al. (1998), in further view of DeWitte et al. (DeWitte R., Shakhnovich E., *J. Am. Chem. Soc.*, 1996, 118: 11733-11744).

Applicant's arguments, filed 4/28/2006, that Zuo et al. do not teach or suggest (i) the use of anything other than a single method of conformational search and scoring, or (ii) a plurality of binding conformations for each ligand. This rejection is maintained for the reasons set forth below. This rejection is maintained for the reasons set forth below.

In response to argument (i): Instant claim 1 recites using "annealing molecular dynamics" and the specification discloses several such programs (e.g. CHARM, AMBER) [0007]. The

instant claims do not require the use of “multiple” methods of conformational searching and scoring. Therefore, the examiner does not find this argument to be persuasive.

In response to argument (ii): Zou et al. use DOCK to identify 10,000 top force field scoring molecules (i.e. a plurality) from the ACD, conduct GB calculations to rank these candidates, use a free energy scoring function to select optimal conformations of a binding ligand [p. 8037, Col. 2, Rank Ordering of Binding Affinities]. Zou et al. also output top ten scoring results according to free energy calculations for a plurality of conformations [Table 4]. For these reasons, the examiner maintains that this is indeed a teaching for a combination of identification, calculation, and selection steps as required by the instantly claimed invention.

Finally, in response to the arguments that Zou et al. do not teach the instantly claimed method, and that Dewitte et al. do not “solve” the argued deficiencies of Zou et al., it is noted that the examiner maintains that Zou et al. do, in fact, teach the claimed invention for the reasons set forth above and in the previous office action. As the examiner maintains that Zou et al. teach the limitations of instant claims 1-6, 8-12, 15, 16, 29, 31, 36-40, and 43-45, as set forth in the previous office action and maintained above, he also maintains that Zou et al. combined with Dewitte et al. make obvious claims 1-6, 8-12, 15, 16, 29, 31, 36-40, and 43-45 for the reasons and motivation previously set forth.

***PRIOR ART MADE OF RECORD***

The prior art made of record and not relied upon which is considered pertinent to applicant's disclosure is:

Rotstein et al. (J. Med. Chem., 1993, Vol. 36, p.1700-1710)

**CONCLUSION**

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pablo S. Whaley

Patent Examiner  
Art Unit 1631  
Office: 571-272-4425

*Marjorie A. Moran*  
7/24/06

**MARJORIE A. MORAN**  
**PRIMARY EXAMINER**